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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The purpose of the work reported here is to develop high-resolution PET instrumentation for imaging the long bones. To-date a single plane prototype and a single plane second-generation instrumentation have been completed. The latter is currently being evaluated. A generalized multi-planar detector element has also been designed and evaluated experimentally and a volumetric instrument has been designed through simulation studies. An radiopharmaceutical for bone growth rate imaging, labeled ^{11}C-tetracycline has been developed for use in a demonstration study of imaging in a monkey osteoporosis model.

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A. Introduction:

The overall aims of this project are:

1. To design and develop an instrument for high resolution PET imaging in long bones.
2. To demonstrate the use of this instrument in an experimental protocol involving the assessment of estrogen therapy for osteoporosis in a monkey model.

We have been granted a one-year extension of the project period without additional funding in order to make further progress in the animal studies originally proposed. We have successfully developed a labeling method for [^{11}C]-tetracycline after having a number of difficulties. Also, a synthesis for ^{18}F-labeled compound has been defined and is in the process of development.

During the current project period we have completed several improvements to the second, final single–plane instrument to improve its performance and have carried out a physical performance evaluation study to characterize it. We have also further explored a design for a generalized volumetric version of the instrument. We have pursued the radiochemical synthesis of 11-C and 18-F tetracycline and have developed a production method for the ^{11}C-labeled compound to define a synthetic approach for ^{18}F labeling. We are currently behind schedule in beginning studies in monkeys due to difficulties with the chemical syntheses but are now in position to begin preliminary studies.

The single plane instruments have been used in a large number of small-animal studies funded under a related DOD project at our institution (DAMD-17-99-1-9555, Dr. A. Brownell, principal investigator).

B. Progress in Tetracycline Labeling:

We have carried out a series of studies to optimize the production of [^{11}C]-tetracycline. Experiments were carried out using two different chemical precursors, two different radioactive precursors and five different solvents as listed in table 1. In each case several experiments were carried out using variations of the steps listed in figure 1 including different evaporation temperatures and times. The aim was to produce the purest possible labeled tetracycline product.

^{11}C methyl iodide ([^{11}C]-CH_3I) was used as a starting point for synthesis in all cases. This precursor is routinely produced at our laboratory and is widely used for the synthesis of 11C-compounds. A system to produce the second precursor, [^{11}C] methyl triflate, from methyl iodide has recently been constructed at our laboratory.

SOLVENTS	CHEMICAL PRECURSORS	RADIOACTIVE PRECURSORS
DMSO Acetonitrile Tetrahydrofluan Acetone Methanol	Tetracycline Hydrochloride Tetracycline Freebase	[^{11}C]-Methyl Iodide [^{11}C]-Methyl Triflate

Table 1: Various solvents, chemical precursors and radioactive precursors evaluated of [^{11}C]-Tetracycline.

Approximately 40 runs were made and analyzed. Typical HPLC spectra of the product, before purification are shown in figures 2-4. The measurements were made using an analytical gradient HPLC system. Figure 2 shows the result for tetracycline hydrochloride precursor, [^{11}C] Methyl Iodide radioactive precursor and Methanol solvent. The labeled tetracycline yield is low, shows two different labeled tetracycline species, and there are many labeled impurities. This is representative of the poorer results obtained. Figure 3 shows a moderately successful result using tetracycline freebase, [^{11}C] Methyl Triflate radioactive precursor and actonitrile solvent. Two labeled tetracycline products are also seen here. Figure 4 shows the result of optimizing the second process above to yield a pure product and predominance of one labeled tetracycline species.

The optimum production process was determined from these experiments as follows: 1.5mg of tetracycline freebase is dissolved in 400ul of acetonitrile. [^{11}C]Methyl Triflate is collected in this solution at room temperature. The resulting mixture is then heated to 60^{0}C for 1 minute and the tetracycline product separated by preparative HPLC.

We are now in a position to begin testing this compound in animals and this will be the main focus of our work during the coming year.

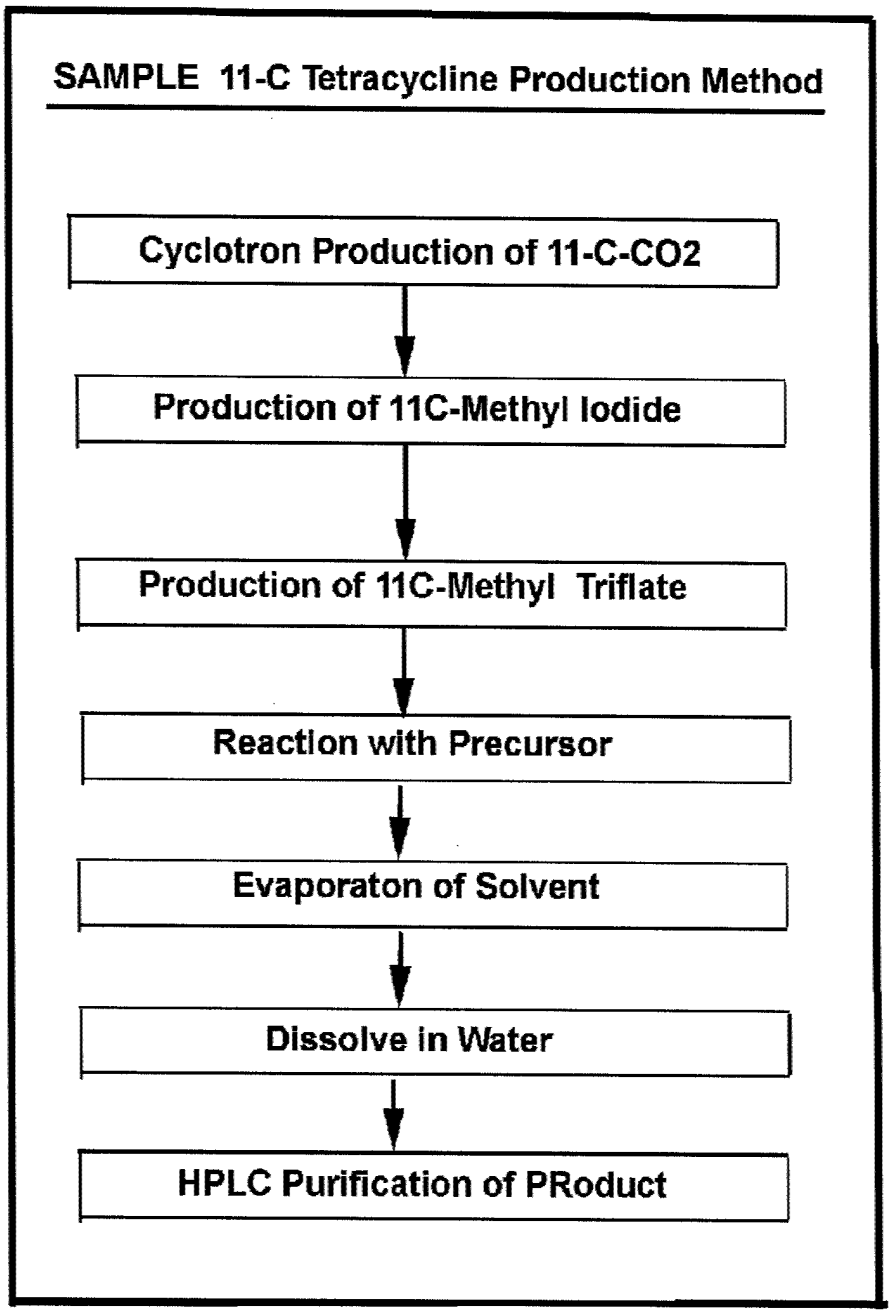


Figure 1: Typical experimental protocol for tetracycline synthesis optimization.

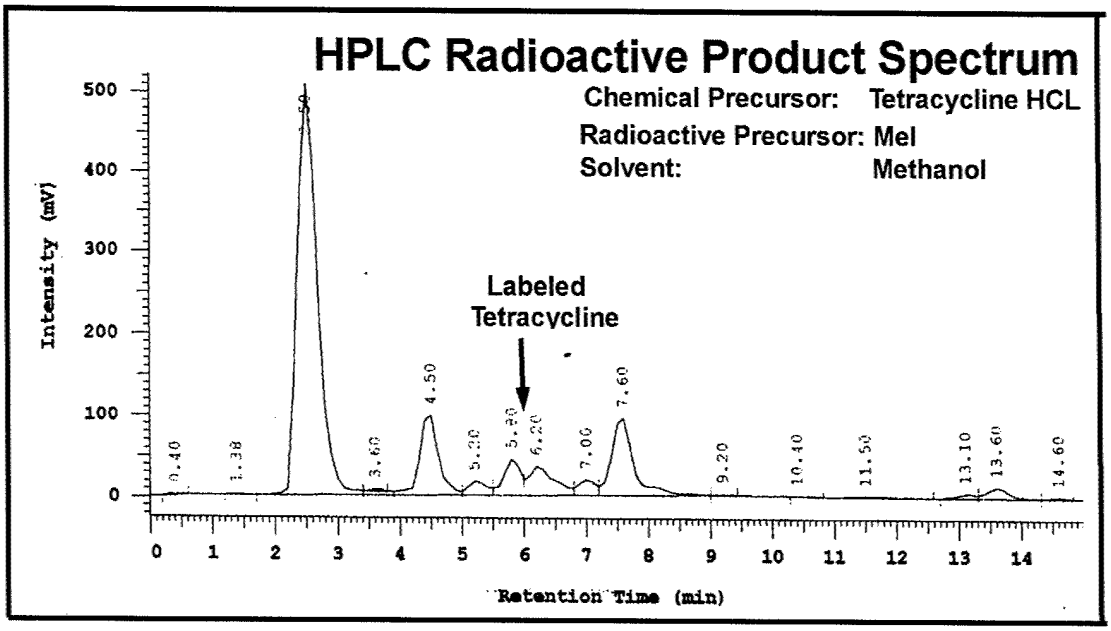


Figure 2: HPLC Radioactive product spectrum. Parameters listed above result in low yield. Results with the same precursors and THF yielded similar results.

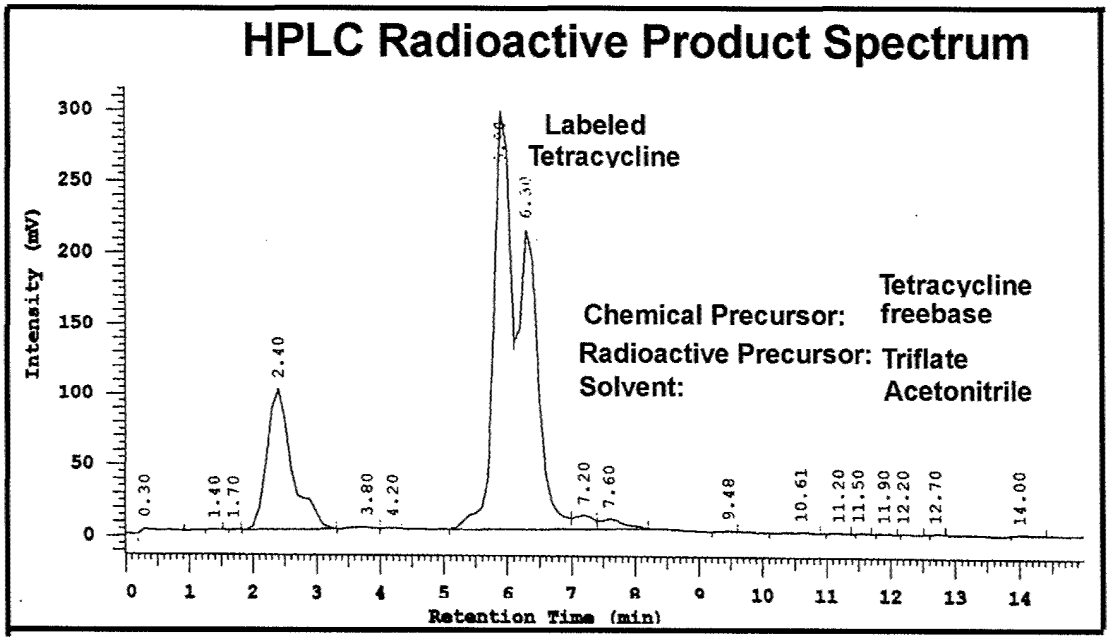


Figure 3: HPLC Radioactive product spectrum. Parameters listed above result in good yield of two labeled tetracyclines

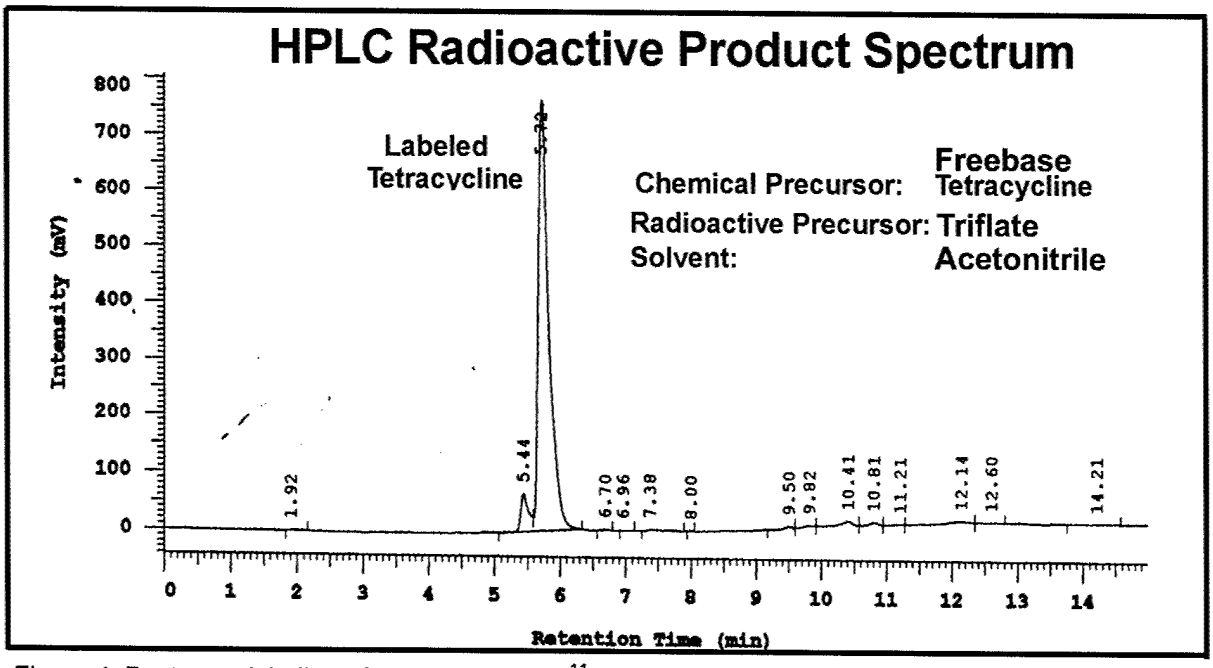
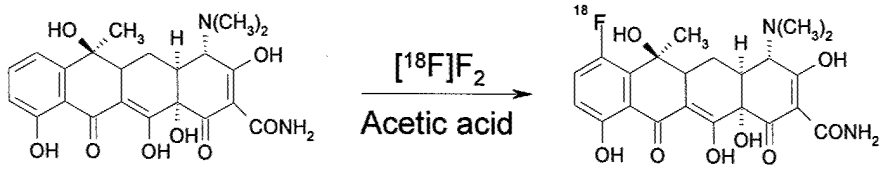


Figure 4: Best case labeling of tetracycline with ^{11}C. The best combination was freebase tetracycline, [^{11}C]-methyl Triflate, and acetonitrile. These resulted in a large majority of a single labeled tetracycline and low levels of other contaminants.

Radiolabelling of Tetracycline with F-18. Tetracycline has several analogs, which have similar physiological functions. Chlortetracycline, for example, has been used as an antibiotic. Furthermore we have labeled tetracycline with ^{131}I (previously reported). Using the similar strategy, tetracycline can be labeled with F-18 using [^{18}F]F_2 gas as the active precursor as shown below.



Labelling of Tetracycline with F-18.

Figure 5: Scheme for labeling tetracycline using [^{18}F]-F_2.

A routine version of this synthesis is currently being developed for use in the project.

C. Status of Instrumentation Development:

Several improvements to the single–plane instrument have been implemented during the past year. These include a method for estimating random coincidences based on system single event rates, improvements to the system electronics which allow a selectable coincidence timing window, modifications to the previously reported data acquisition interface to minimize event losses due to interference between the computer hardware resulting from timing conflicts between front-end buffer transfers and the periodic behavior of the PCI bus interface. This allows operation at higher counting rates with acceptable dead-time losses. Also, several dedicated off-board computers with real time operating systems (RTOS) have been temporarily integrated into the system to evaluate their use in making data acquisition completely independent of the main computer's operating system thus eliminating conflicts entirely.

As a central part of this project we have designed and constructed two single plane small Animal PET instruments with spatial resolution of approximately 1mm. The detector elements of the first (prototype) system consisted of blocks of 12 1x5x4.5 mm LSO crystals with each block spanning two adjacent phototubes in a 30 phototube ring. This system performed well but was limited by low sensitivity due the short crystal depth and by effects of light losses at the centers of the blocks. To moderate these limitations we designed and constructed a second-generation (final) system in which the crystal elements were modified to 1.2x7x4.5mm and organized into blocks of 10 crystals. These modifications lead to improved light collection compared to the first generation system (from 50-65%) and better identification of the end crystals. We have undertaken a systematic physical evaluation of the final instrument (accepted for publication, IEEE, 2002). Some representative results of this study are given below.

The in-plane spatial resolution was measured with small-diameter (0.4mm) ^{18}F-line sources and the results are given in figure 6. The measured in-plane resolution is 1.25mm FWHM at the center of the field and 1.5mm FWHM at two-cm radius. The FWTM is also illustrated in figure 6. The measured system sensitivity for both a point source and a 4.5cm cylindrical source are shown in table 2. They are compared to the same quantities for the prototype instrument. A twofold increase in sensitivity results from a combination of increased crystal thickness, improved event identification at the block centers and an increase in detector ring diameter from 12.4 to 14.7cm.

Figure 7 shows a measurement of the axial resolution of the instrument made using a 1mm-diameter point source of ^{68}Ge and a 4.5mm axial aperture. This aperture can be reduced to provide thinner slices by changing the shielding collimator. In this mode the central axial resolution was measured to be 1.9mm and the resolution at 2 cm radius was 2.3mm.

Figure 8 shows two measurements of scatter fraction for 3.8cm and 6cm tissue equivalent scattering cylinders containing a line source of ^{18}F at their centers. The measured scatter fraction for the smaller cylinder, .019, is slightly less than

that of the first generation instrument as would be expected due to the increased ring diameter.

Figure 9 shows an example of the instrument's performance in an extended object, a high-resolution Micro-Jaczczak phantom. The data are not scatter corrected. The 1.5mm cold rods are well separated and a hint of the 1-mm rods can be seen near the object center. This is phantom, which is a distribution of cold (non-radioactive) rods of differing sizes in a radioactive background is an extremely rigorous test of instrument image quality.

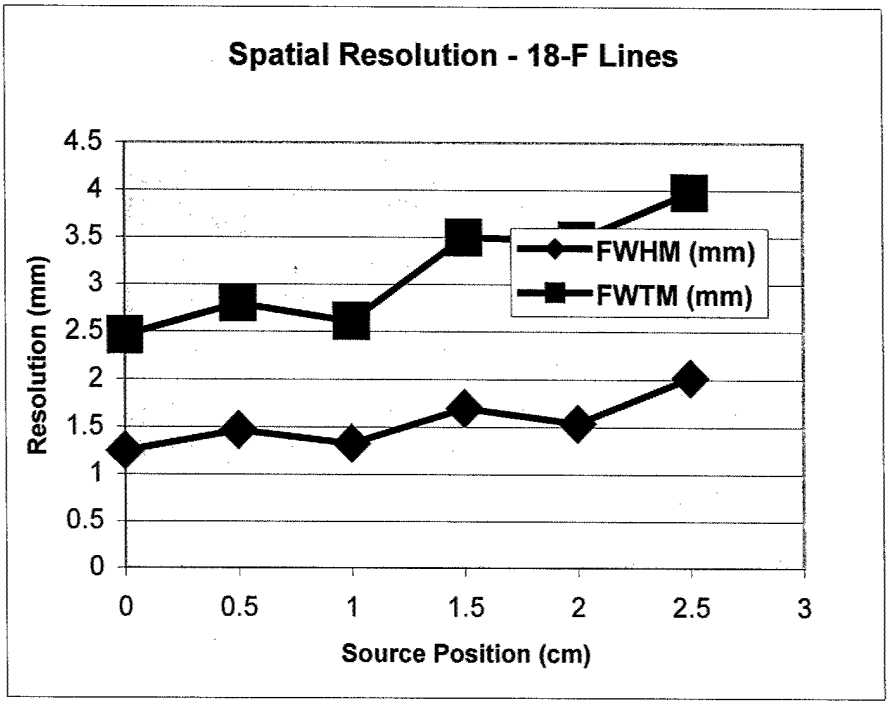


Figure 6: Spatial resolution as a function of field radius measured with 0.42mm 18-F line sources. Measurements are corrected for source size. FWHM and FWTM shown.

MMP Generation	Prototype	Final
Point (cpm/uCi)	30	56
4.5cm Cylinder (cpm/uCi/cc)	204	398

Table 2: Comparison of measured sensitivities for first and second-generation instruments. Both measurements made with 18-F.

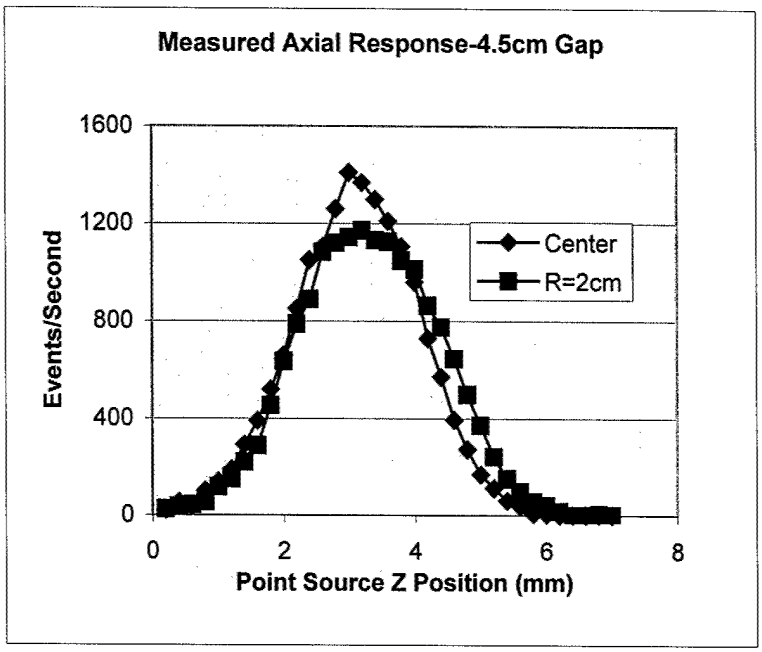


Figure 7: Axial resolution measurements at field center and 2cm radius for 4.5cm z-gap. 18-F point source was stepped at 0.1-mm steps axially through the field.

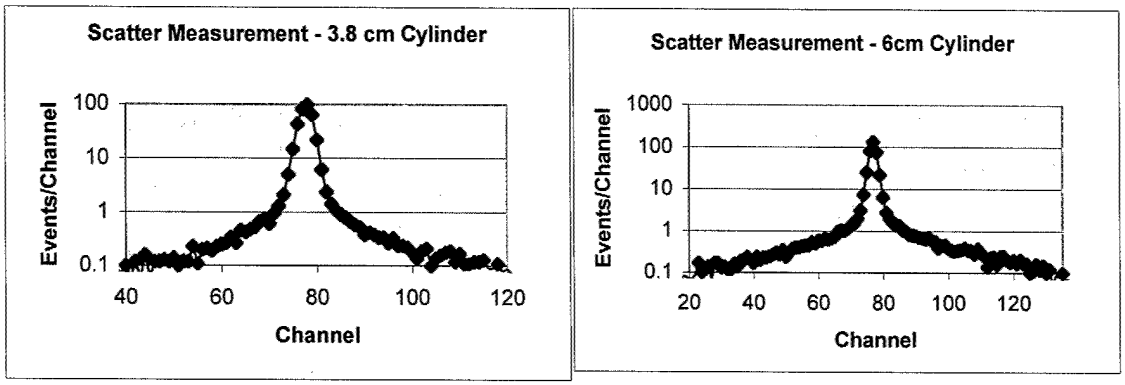


Figure 8: Measurement of scatter distribution from a line source of 18-F at the center of two different sized absorbers. Shown is the sum of the projection data over all angles(i.e., integration of the sinogram over angle). The measured scatter fraction is .019 for the 3.8cm absorber and .048 for the 6-cm absorber.

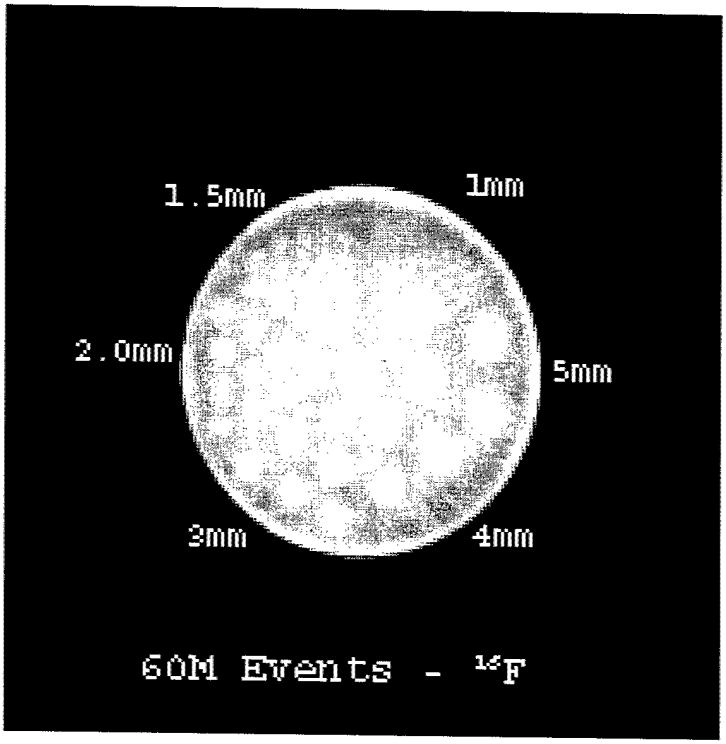


Figure 9: Image of a high-resolution Micro-Jaszczak cold spot phantom (diameter 4.5cm) filled with 18-F. The cold rod sizes are indicated.

A second-generation single-plane small animal PET has been completed and its properties evaluated experimentally. The design goals of higher sensitivity and better detector block performance have been met.

The design studies of the volumetric instrument reported previously have been completed and separate funding is being sought to build a prototype system. Several new detector module designs are being considered to extend the axial extent of the instrument. The overall approach is to introduce partially opaque optical interfaces axially at various positions along the crystal array in order to control light spreading. This concept is illustrated in figure 10 below. The amount of reflectivity/transmissivity of the surfaces will define axial light distribution and hopefully moderate end effects. Simulation studies of the optics of these detector modules have been begun and will be continued during the next year.

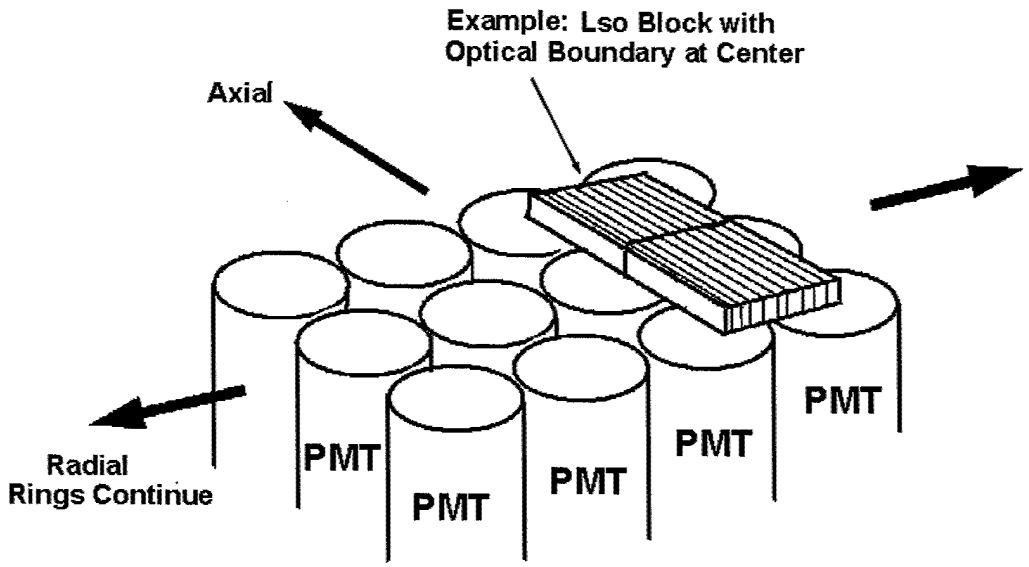


Figure 10: Sketch of a possible three phototube-ring instrument with long blocks having an axial optical boundary at the center to control light shaping.

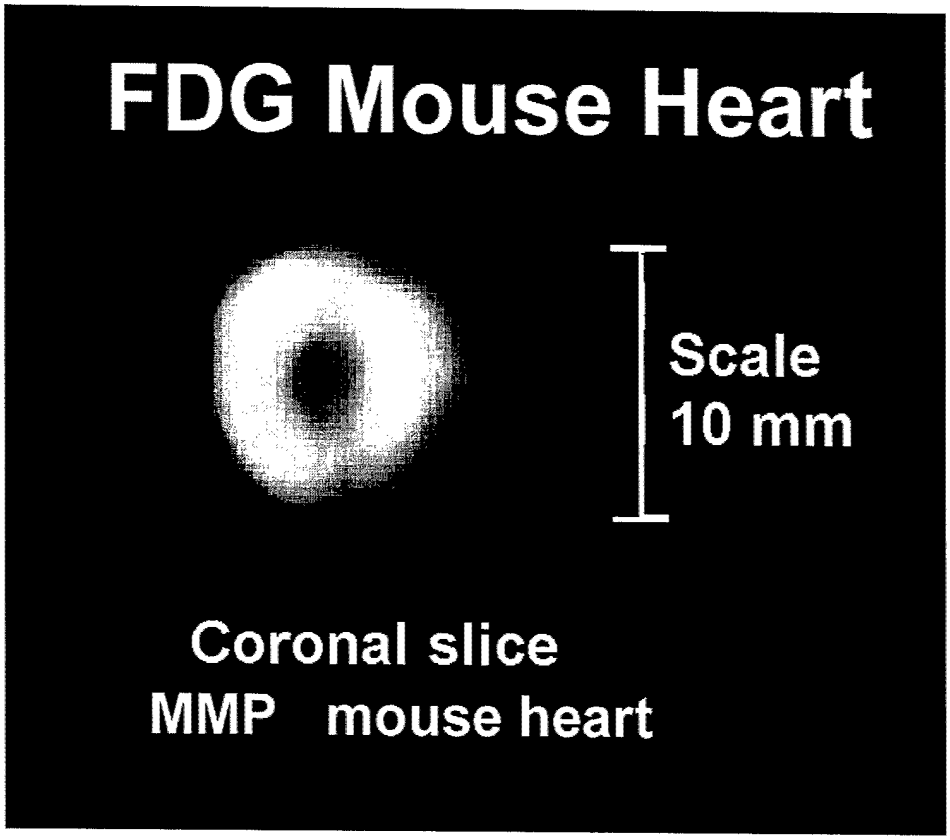


Figure 11: Image of mouse myocardium and enclosed ventricle after injection of FDG.

D. Animal Studies Carried out by Related DOD Projects Using Instruments:

A DOD-funded project at our institution which is closely related this one is DAMD17-99-1-9555 entitled "Evaluation of Early and Prolonged Effects of Neurotoxicity using Functional Imaging Techniques" (A.L. Brownell, P.I.) Studies of small animals under that program using the instrumentation developed by our effort are part of their aims. During the last year Dr. Brownell and her co-workers have carried out approximately 100 rat and mouse imaging studies. A particularly interesting example, that of a mouse heart imaged after injection of ^{18}F-fluorodeoxyglucose, is shown in figure 11. The high-resolution capability of the instruments developed in this project is demonstrated by our ability to see the myocardial wall and ventricle in this very small (25gm) creature.

VI. Key Research Accomplishments:

1. Improvements of single plane PET instrument.

2. Performance Evaluation of final instrument.

3. Development of routine synthesis of ^{11}C-tetracycline.

4. Completion of a design for a volumetric generalization of the single plane instrument.

VII. Reportable Outcomes:

1. Construction of single-plane 1mm resolution PET instruments. Published, patent being pursued through MGH.

2. Completion of Volumetric block design. Partially published. Patent on detector module design being pursued.

3. Design of Volumetric PET instrument. In Press. Patent on Instrument being pursued.

4. Development of a routine synthesis for [^{11}C]-tetracycline. Publication in preparation.

VIII. Conclusions:

During the first year of the project we established the design of a high resolution PET instrument for bone imaging and constructed a prototype. During the second year we physically characterized the prototype, modified our design and began construction of a final single plane device. The construction of this device was completed in the current year. Beginning in the second year and we developed a generalized detector element and a system design for multi-planar (or volumetric) imaging. During year 3 and the current year we have worked on the development of labeled tetracycline for bone imaging. In year 2 we successfully labeled it with iodine and carried out biodistribution studies in rats. A number of approaches to 11-C labeling were explored and a routine synthesis established in the current reporting year. An approach to labeling with ^{18}F has been established and is being pursued. We are now in a position to begin preliminary animal studies and will do so in the next few months.

VI. Appendix.

Previously Reported Publications:

1. "Development of a Small Animal Pet Imaging Device with Resolution Approaching 1mm", JA Correia, CA Burnham, D Kaufman, AJ Fischman, J Nucl Med 40:285P (1999) Abstr.

2. "Development of a Small Animal Pet Imaging Device with Resolution Approaching 1mm", JA Correia, CA Burnham, D Kaufman, AJ Fischman, IEEE Trans Nucl Sci 46:631-635 (1999).

3. "A Pet Imaging Instrument for High Resolution Rat and Mouse Imaging ", JA Correia, CA Burnham, D Kaufman, E. Carter, AL Brownell, AJ Fischman, "High Resolution Imaging in Small Animals with PET, MRI and other Modalities: Proceedings", pp 63-64, Amsterdam (1999).

4. "Performance of a Small Animal Pet Imaging Device with Resolution Approaching 1mm", JA Correia, CA Burnham, D Kaufman, AJ Fischman, IEEE Nuclear Science Symposium and Medical Imaging Conference Record, M7:pp 1-5 (1999).

5. "Designs for Small Animal PET Systems" ,Abstr., JA Correia, CA Burnham, D Kaufman, AJ Fischman, Congress of European Assoc. Nuclear Med, (Sept, 2000).

6. Design Considerations for Small-Animal PET Devices with Resolution Approaching 1 mm", JA Correia, CA Burnham, D Kaufman, AJ Fischman, , IEEE Nuclear Science Symposium and Medical Imaging Conference Record,pp 21:41-45 (2001).

7. " Design of a Volumetric High Resolution Small Animal PET ", JA Correia, CA Burnham, D Kaufman, AJ Fischman, "High Resolution Imaging in Small Animals: Proceedings", pp 187-188, (2001).

8. " An LSO-based detector element for a Multiplanar small animal PET instrument", JA Correia, CA Burnham, D Kaufman, AJ Fischman, J Nucl Med 41:56P (2001) Abstr.

New Publications Since Last Report:

9. *" Design Studies for a Volumetric High Resolution Small Animal PET ", JA Correia, CA Burnham, D Kaufman, AJ Fischman, " IEEE Trans Nucl. Sci",, (2002).*

10. *4. "Performance Evaluation of a second-generation single-plane small animal imaging instrument", JA Correia, CA Burnham, D Kaufman, AJ Fischman, IEEE Trans. Nuclear Science (2002) (in press).*